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An Efficient Copper-Catalyzed Carbon−Sulfur Bond Formation Protocol in Water

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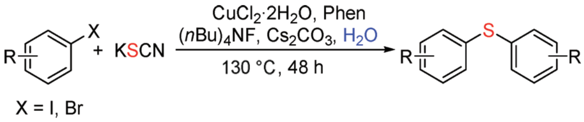
ABSTRACT



An efficient protocol of copper-catalyzed C−S bond formation between aryl halides and potassium thiocyanate leading to diaryl sulfides is reported. A variety of diaryl sulfides can be synthesized in good to excellent yields up to 94%.

The development of new, efficient, and environmentally benign synthetic methodologies for the construction of complex molecules is an important target in modern organic synthesis.[1] Diaryl sulfide functionalities have been found in numerous drugs with a broad spectrum of therapeutic activities such as antidiabetes, anti-inflammatory, anti-Alzheimer's, anti-Parkinson's, anticancer, and anti-HIV.[2] However, the related C−S bond formation reactions are less studied compared with C−N and C−O processes, which is partially caused by the fact that organic sulfur compounds have a tendency to bind to metals, acting as metal deactivators.[3] Originally, the traditional methods for the formation of C−S bonds take place in polar solvents, such as HMPA, and at elevated temperatures around 200 °C.[4] To overcome these drawbacks, transition-metal-catalyzed coupling systems have been explored. Migita et al. first reported cross-coupling reactions of aryl halides with thiols in the presence of $Pd(PPh_3)_4$ in their seminal work in 1980.[5] Recently, nickel,[6] palladium,[7] iron,[8] and cobalt[9] catalysts have emerged as appealing catalysts for this reaction.

Copper salts have also been used as alternative and promising catalysts for many organic transformations including C−S bond forming reaction.[10]

On the other hand, the common methods for the assembly of diaryl sulfides are based on the condensation of aryl halides with thiols or metal sulfides. Less common synthetic strategies involve the transformation of thiourea or disulfides.[11] Still and Toste reported that direct preparation of diaryl sulfides could be achieved *via* the reaction of samarium thiolates with aryl

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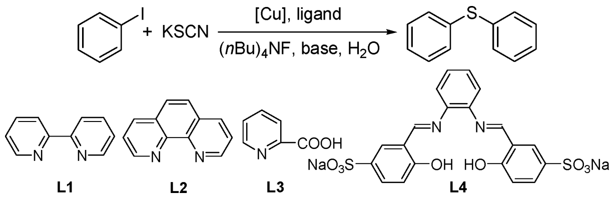
halides in THF.[12] Moreover, thiocyanate is more stable than the above-mentioned sulfur sources and has usually been used as a sulfur transfer reagent in organic transformation.[13] Inspired by these encouraging results, we considered the application of metal thiocyanates in the coupling reaction.

Furthermore, the use of water as solvent in organic reactions has attracted much attention in recent years due to the low cost, nontoxicity, safety, and environmental friendliness compared with organic solvents.[14] As part of our endeavors to develop aqueous catalysis,[15] herein is reported the efficient C−S bond formation between potassium thiocyanate and aryl halides by a copper catalyst in water.

Initially, iodobenzene and potassium thiocyanate were selected as model substrates during the optimization of reaction conditions. As shown in Table 1, among the different ligands **L1**−**L4**, **L2** (1,10-phenanthroline) exhibited the highest catalytic activity in 92% yield (Table 1, entries 1−4). Comparison of different copper sources indicated that $CuCl_2{\cdot}2H_2O$ and CuI were superior to others including $Cu(OAc)_2{\cdot}H_2O$, $CuSO_4{\cdot}5H_2O$, CuO, and Cu_2O (Table 1, entries 5−9). A range of bases including Cs_2CO_3, KOH, K_2CO_3, K_3PO_4, NaOH, and Na_2CO_3 were screened, and Cs_2CO_3 gave the best result (Table 1, entries 10−14). Further studies revealed the optimal reaction temperature to be 130 °C and reaction time to be around 48 h (Table 1, entries 15−19). Meanwhile, control experiments proved the essential presence of metal and PTC ($(n\mathrm{Bu})_4NF$) (Table 1, entries 20−21). Therefore, the optimal catalytic system involved the use of $CuCl_2{\cdot}2H_2O$ (10 mol %), **L2** (10 mol %), $(n\mathrm{Bu})_4NF$ (20 mol %), and Cs_2CO_3 (2 equiv) in water at 130 °C for 48 h.

Table 1. Optimization of Reaction Conditions in the Copper-Catalyzed Coupling of Iodobenzene and Potassium Thiocyanate[a]

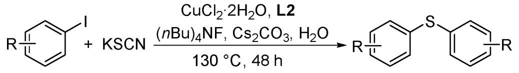


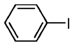
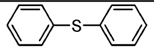
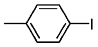
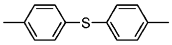
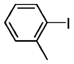
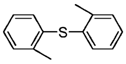
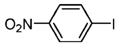
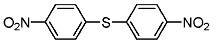
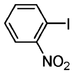
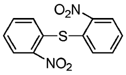
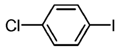
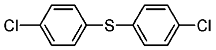
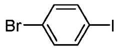
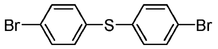
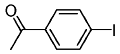
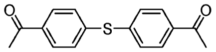
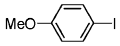
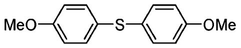
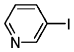
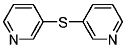
entry	[Cu] source	ligand	base	t(h)	temp(°C)	yield(%)[b]
1	CuI	**L1**	Cs_2CO_3	48	130	52
2		**L2**	Cs_2CO_3	48	130	92
3		**L3**	Cs_2CO_3	48	130	33
4		**L4**	Cs_2CO_3	48	130	45
5	$Cu(OAc)_2{\cdot}H_2O$	**L2**	Cs_2CO_3	48	130	39
6	$CuSO_4{\cdot}5H_2O$	**L2**	Cs_2CO_3	48	130	42
7	$CuCl_2{\cdot}2H_2O$	**L2**	Cs_2CO_3	48	130	94
8	CuO	**L2**	Cs_2CO_3	48	130	20
9	Cu_2O	**L2**	Cs_2CO_3	48	130	17
10	$CuCl_2{\cdot}2H_2O$	**L2**	NaOH	48	130	60
11		**L2**	Na_2CO_3	48	130	26
12		**L2**	KOH	48	130	58
13		**L2**	K_2CO_3	48	130	63
14		**L2**	K_3PO_4	48	130	44
15		**L2**	Cs_2CO_3	48	120	83
16		**L2**	Cs_2CO_3	48	140	90
17		**L2**	Cs_2CO_3	24	130	60
18		**L2**	Cs_2CO_3	36	130	86
19		**L2**	Cs_2CO_3	60	130	89
20[c]		**L2**	Cs_2CO_3	60	130	9
21		**L2**	Cs_2CO_3	60	130	trace

[a] Reactions were carried out using iodobenzene (1.0 mmol), KSCN (1.5 mmol), Cu source (0.1 mmol), ligand (0.1 mmol), base (2.0 mmol), and $(n\mathrm{Bu})_4NF$ (0.2 mmol) in water (5 mL). [b] Determined by GC using 1,4-dichlorobenzene as internal standard. [c] Without addition of $(n\mathrm{Bu})_4NF$.

Then, a number of aryl iodides were examined to explore the scope of substrates. As shown in Table 2, different aryl iodides were transformed into the corresponding diaryl sulfides in moderate to excellent yields ranging from 69% to 94%. Steric hindrance seemed to have an effect on the results. For example, *p*-iodotoluene and *p*-nitroiodobenzene gave the desired products in 90% yields, while 83% and 85% yields were obtained in the case of *o*-iodotoluene and *o*-nitroiodobenzene as substrates (Table 2, entries 2−5). Moreover, 78% and 79% yields obtained

Table 2. Copper-Catalyzed C−S Coupling of Different Aryl Iodides with Potassium Thiocyanate[a]



entry	aryl iodide	product	yield (%)[b]
1			94
2			90
3			83
4			92
5			85
6			78
7			79
8			87
9			81
10			69

[a] Reactions were carried out using aryl iodide (1.0 mmol), KSCN (1.5 mmol), $CuCl_2{\cdot}2H_2O$ (0.1 mmol), **L2** (0.1 mmol), Cs_2CO_3 (2.0 mmol), and $(n\mathrm{Bu})_4NF$ (0.2 mmol) in water (5 mL) at 130 °C for 48 h. [b] Isolated yield after chromatography.

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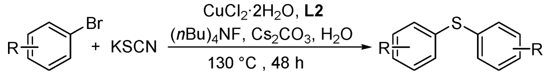
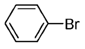
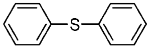
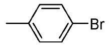
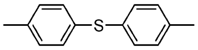
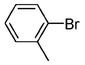
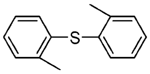
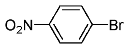
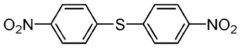
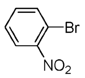
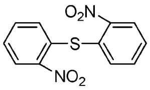
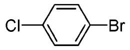
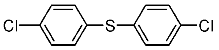
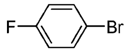
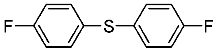
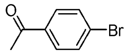
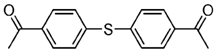
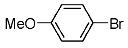
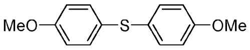
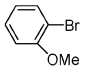
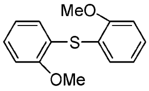
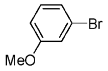
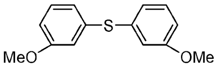
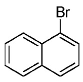
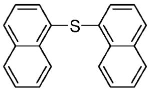
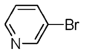
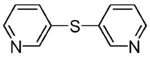
in the case of *p*-chloroiodobenzene and *p*-bromoiodobenzene implied that there was good chemoselectivity between iodide, bromide, and chloride functional groups (Table 2, entries 6, 7). Furthermore, the catalytic system could well tolerate a variety of functional groups, including ketone, and hydroxymethyl groups (Table 2, entries 8, 9). A heterocyclic compound, such as 3-iodopyridine, could also afford the corresponding product in 69% yield (Table 2, entry 10).

Aryl bromides could also react with potassium thiocyanate under the same reaction conditions albeit in slightly lower yields than aryl iodides, and the results were listed in Table 3. Another reaction by using chlorobenzene as a substrate gave only 5% product under the same conditions, which proved the inactivity of the C−Cl bond in this catalysis.

Table 3. Copper-Catalyzed C−S Coupling of Different Aryl Bromides with Potassium Thiocyanate[a]

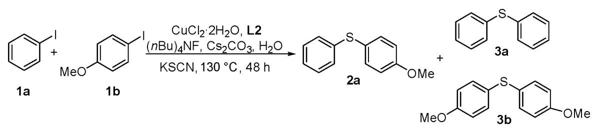


entry	aryl bromide	product	yield (%)[b]
1			83
2			72
3			69
4			75
5			60
6			70
7			32
8			77
9			51
10			42
11			49
12			73
13			64

[a] Reactions were carried out using aryl bromide (1.0 mmol), KSCN (1.5 mmol), CuCl$_2$·2H$_2$O (0.1 mmol), **L2** (0.1 mmol), Cs$_2$CO$_3$ (2.0 mmol), and (nBu)$_4$NF (0.2 mmol) in water (5 mL) at 130 °C for 48 h. [b] Isolated yield after chromatography.

Next, we tried the possibility of applying this catalytic system in the cross-coupling reaction between two different aryl halides by using iodobenzene and 4-methoxyiodobenzene as model substrates. As shown in Table 4, when the ratio of two substrates was 1:1, only 37% cross-coupling product was obtained, while the symmetric products were found to be the main side product as expected (Table 4, entry 1). To improve the results, the ratio of substrates was increased to 1:3 and 1:5, and the corresponding yields resulted in 58% and 74% respectively (Table 4, entry 2−3). The catalytic system was then extended to other substrates and afforded moderate to good yields (Table 5) (see the Supporting Information).

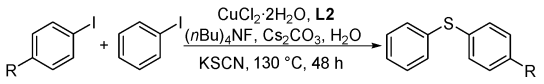
Table 4. Cross-Coupling of Aryl Iodides Catalyzed by Cu[a]

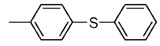
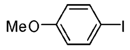
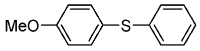
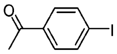
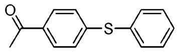
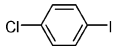
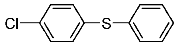


entry	1a	1b	**2a** yield(%)[b]	**3a** yield(%)[c]	**3b** yield(%)[d]
1	1.0	1.0	37	52	41
2	1.0	3.0	58	25	57
3	1.0	5.0	74	8	64

[a] Reactions were carried out using KSCN (3.0 mmol), CuCl$_2$•2H$_2$O (0.1 mmol), **L2** (0.1 mmol), Cs$_2$CO$_3$ (2.0 mmol), and (nBu)$_4$NF (0.2 mmol) in water (5 mL) at 130 °C for 48 h. [b] Isolated yields based on 1.0 mmol of reactant. [c] Yields based on **1a**. [d] Yields based on **1b**.

Table 5. Copper-Catalyzed Cross-Coupling Reaction of Different Aryl Iodides[a]



entry	aryl iodide	product	yield (%)[b]
1			82
2			74
3			78
4			76

[a] Reactions were carried out using aryl halide (5 mmol), iodobenzene (1 mmol), KSCN (3.0 mmol), CuCl$_2$•2H$_2$O (0.1 mmol), **L2** (0.1 mmol), Cs$_2$CO$_3$ (2.0 mmol), and (nBu)$_4$NF (0.2 mmol) in water (5 mL) at 130 °C for 48 h. [b] Isolated yields based on 1.0 mmol of reactant.

At last, this catalytic system was extended to the synthesis of 2-phenylsulfanylbenzamide, which was reported to exhibit SIRT1 (an NAD$^+$-dependent protein deacetylase) inhibitory activity.[16] As shown in Scheme 1, the product could be

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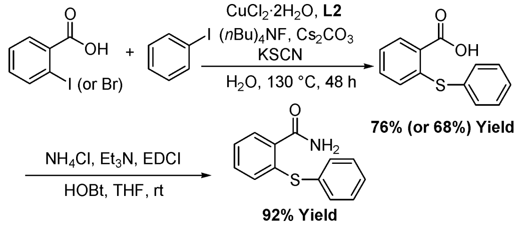
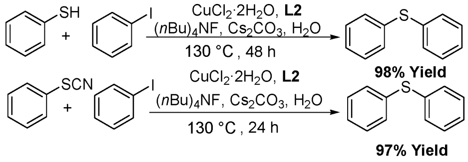
Scheme 1. Synthesis of 2-Phenylsulfanylbenzamide in Water



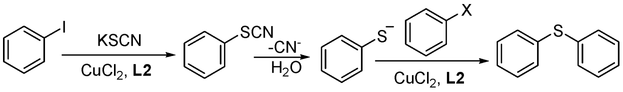
conveniently obtained from the reaction of 2-iodobenzoic acid or 2-bromobenzoic acid with iodobenzene, followed by treatment with EDCI and HOBt in ~70% total yield. This two-step reaction contributed an alternative way to access 2-phenylsulfanylbenzamide derivatives.

Furthermore, during our investigation of the catalytic pathway, the presence of H_2O was found to be essential for the catalysis, while only a trace of product could be obtained by using organic solvents including DMSO or THF either with or without PTC. The existence of thiophenol and phenyl thiocyanate detected by GC/MS during reaction suggested the dissociation of PhSCN during the catalysis. Control experiments between thiophenol and PhSCN with iodobenzene afforded the coupling product in 98% and 97% yields respectively under the optimal catalytic conditions (Scheme 2). Based on these results and literature,[13a,16] the reaction pathway is assumed as shown in Scheme 3. First, an aromatic halide is activated by a Cu(II) complex, leading to the formation of aryl thiocyanate. Then, aryl thiocyanate is hydrolyzed to generate a thiolate ion, which reacts with the aryl halide to afford the C−S coupling product, and CN^- is hydrolyzed by a base under the reaction conditions.[17,18]

Scheme 2. Reaction of Iodobenzenes with Thiophenol and Phenyl Thiocyanate



Scheme 3. Proposed Catalytic Pathway for the C−S Formation



In conclusion, we have developed an effective copper catalytic system for the reaction of aryl halides and potassium thiocyanate in neat water without inert reaction conditions. A variety of aryl halides could be reacted with potassium thiocyanate to give the desired products in high yields up to 94%. 2-Phenylsulfanylbenzamide derivatives could be efficiently synthesized by this method. Further applications to the synthesis of biologically important molecules and mechanism studies are in progress.

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Supporting Information Available: Detailed procedure and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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